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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,247	08/14/2006	Tatsuya Nakai	294136US0X PCT	6936

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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.
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EXAMINER	
CHUI, MEI PING	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
06/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/589,247	NAKAI ET AL.	
	Examiner	Art Unit	
	MEI-PING CHUI	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2009 and 06 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7-14,17-22 and 24-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7-14,17-22 and 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Action

Receipt of Amendments/Remarks filed on **02/23/2009** is acknowledged. Claims 1, 4, 7-24 are pending in the application. Claims 1, 4, 7-9 have been amended; claims 2-3, 5-6 have been cancelled; new claims 10-24 are added.

Receipt of Supplement Amendments/Remarks filed on **03/06/2009** is acknowledged. Claims 1, 4, 7-14, 17-22, 24-27 are pending in the application. Claims 1, 4, 7-14, 17-22, 24 are previously presented; claims 2-3, 5-6, 15-16, 23 have been cancelled; new claims 25-27 are added.

Upon further consideration and search, Applicants' amendments necessitated the new grounds of rejection presented in this Office Action. Accordingly, this action is made FINAL.

Status of Claims

Accordingly, claims **1, 4, 7-14, 17-22, 24-27** are presented for examination on the merits for patentability.

Rejection(s) not reiterated from the previous Office Action are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

New Grounds of Claim Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

(1) Claims 1, 4, 7-14, 17-20, 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katsuma et al. (EP 0682942 A1) in view of Osborne et al. (U. S. Patent No. 6,432,415).

Applicants Claim

Applicants claim an external preparation comprising: (**A**) atorvastatin, pitavastatin, or a salt thereof (0.001-20 % by mass relative to the total amount of the external preparation) and (**B**) at least one monoterpene (0.01-15 % by mass relative to the total amount of the external

preparation), i.e. menthol, terpineol or citronellal, or a combination thereof, and wherein the preparation does not contain ethanol.

Determination of the scope and content of the prior art

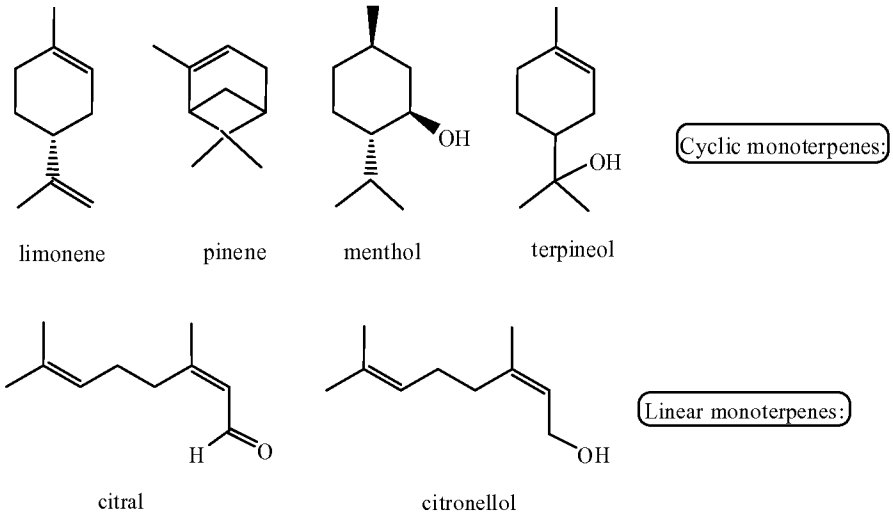
(MPEP 2141.01)

Katsuma et al. teach a novel transdermal therapeutic preparation, which can efficiently deliver a pharmaceutically active agent into the living body. Katsuma et al. teach that the transdermal preparation is a highly safe and administration-controllable delivery system, in which the transdermal drug absorption-enhancing property of highly safe terpenes is effectively exerted in the delivery system without causing irritation to the skin, even in the presence of ethanol as solvent (page 2, lines 3-5 and 50-58).

Katsuma et al. also teach that the transdermal absorption preparation comprises a pharmaceutical active agent for hyperlipemia use, i.e. simvastatin, pravastatin sodium and the like (page 5: line 26). In addition, Katsuma et al. teach that the active drugs can be used alone, or as a mixture of two or more, in an amount sufficient to exert desired drug effects, wherein the amount of the active drug can be presented within the range from 0.01 % to 20 % by weight, based on the weight of the composition (page 5, lines 26, 36-37; page 5, line 38).

Katsuma et al. further teach that the transdermal absorption preparation also comprises a monoterpene, or a combination of monoterpene, which acts as a transdermal absorption enhancing agent, wherein the monoterpene can be from essential oils that contain monoterpenes as main components (page 3, lines 9 and 20). Katsuma et al. further teach that suitable monoterpenes can be those having cyclic hydrocarbon structures, i.e. limonene and pinene, or

linear monoterpenes having an aldehyde or a hydroxyl group, i.e. citral or citronellol. In addition, cyclic monoterpenes having a hydroxyl group, i.e. 1-menthol and terpineol, are also useful as the transdermal absorption enhancing agent (page 3, lines 9-20 and 36-40, and structures below):



Katsuma et al. then teach that the monoterpenes can be presented in an amount from 1 % to 50 % by weight, preferably from 1 % to 10 % by weight, relative to the total weight of the transdermal preparation (page 3, lines 23-24 and page 5, line 38).

Katsuma et al. also teach that the transdermal absorption preparation is for external purpose (page 5, line 48), in which the external preparation dramatically improves the skin penetration of drugs that are generally considered having relative low skin penetration ability to a great extent (page 21, lines 9-12).

With respect to the recitation of the external preparation of claim 1 is a plaster or a poultice, as claimed in claims 18 and 19, it is noted that the prior art Katsuma et al. do not teach

that the transdermal absorption preparation is used in the same manner as claimed in claims 18-19; however, the intended use of the claimed external preparation does not patentably distinguish the composition, per se, since such undisclosed use is inherent in the reference composition. In order to be limiting, the intended use must create a structural difference between the claimed composition and the prior art composition. In the instant case, the intended use does not create a structural difference, thus the intended use is not limiting.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

(**1**) However, Katsuma et al. do not explicitly teach the calcium salt of pravastatin or the calcium salt of atorvastatin, as instantly claimed.

(**2**) Katsuma et al. also do not teach the monoterpene citronellal, which is a monoterpene containing an aldehyde functional group, as instantly claimed.

(**3**) Katsuma et al. teach the transdermal absorption preparation containing ethanol as a solvent, whereas the instantly claimed external preparation recites the preparation does not contain ethanol. This deficiency is cured by the teaching of Osborne et al.

Osborne et al. teach a bio-adhesive formulation, i.e. pharmaceutical gel formulation or dermatological formulation that are capable of delivering drugs of varying solubility characteristics, wherein the formulations are suitable for applying to a skin surface (Abstract and column 2, lines 20-24; column 12, lines 48-50).

Osborne et al. teach that from a practical point-of-view, increased water content is desirable because when a subject administers a formulation to the skin or mucosal surfaces, it is

desirable that the formulation is not dehydrating and preferably moisturizing to prevent not only topical reactions to the formulations but also to keep the formulation adhering to the application site. Formulations containing non-aqueous solvents such as ethanol may give rise to this problem because ethanol is a dehydrating agent.

Finding of prima facie obviousness Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to a person of ordinary skilled in the art at the time the invention was made to combine the teaching of Katsuma et al. and Osborne et al. to arrive at the instant invention.

(1) One of ordinary skill would have been motivated to select a hyperlipemia drug, i.e. pravastatin or atorvastatin, or the salt thereof, and reasonably expect a similar and successful result because pravastatin or atorvastatin, or their salts, are all effective hyperlipemia drugs for lowering cholesterol. Therefore, they are functional equivalent hyperlipemia drugs and can be used interchangeably in combination with a monoterpene to formulate the external preparation.

(2) One of ordinary skill would have been motivated to utilize the monoterpene citronellal instead of citral because citronellal and citral are structural and functional equivalent monoterpenes (both contain aldehyde functional group), and thus can be used interchangeably to formulate the external preparation.

(3) One of ordinary skill would have been motivated to avoid the use of ethanol in a topical formulation, i.e. a dermatological formulation, because it is known in the art that ethanol is a dehydrating agent and may give undesirable effect to the skin by removing excessive amount of moisture content from the skin, as taught by the prior art Osborne et al. Therefore, one of

ordinary would have been motivated to devoid the use of ethanol in the instantly claimed preparation, as suggested by the prior art Osborne et al.

In the absence of evidence to the contrary, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed external formulation, which comprises a hyperlipemia drug (i.e. pravastatin calcium) and a monoterpene that performs the same as the transdermal absorption preparation taught by the prior art Katsuma et al. Therefore, the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference.

(2) Claims 21-22, 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katsuma et al. (EP 0682942 A1) and Osborne et al. (U. S. Patent No. 6,432,415), and further in view of Sawayanagi et al. (U. S. Patent No. 5,296,235) and Hidaka et al. (U. S. Patent No. 5,225,199) combined.

Applicants Claim

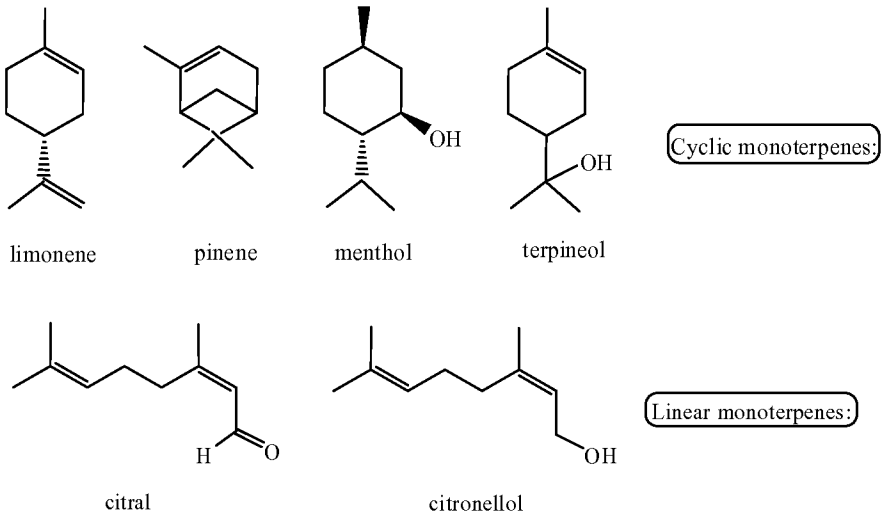
Applicants claim an external preparation comprising: (**A**) pitavastatin calcium and (**B**) a monoterpene, i.e. menthol, wherein the external preparation is a plaster or a poultice. Applicants also claim that the external preparation further comprises liquid paraffin, a styrene-isoprene-styrene copolymer, an alicyclic saturated hydrocarbon resin, and a polyoxyethylenelaurylether; or the external preparation further comprises polyethylene glycol, glycerin, carmellose sodium, magnesium alumino-metasilicate, sodium polyacrylate, partially neutralized polyacrylic acid, tartaric acid, kaolin, D-sorbitol, and water.

Determination of the scope and content of the prior art

(MPEP 2141.01)

The teachings of Katsuma et al. and Osborne et al. have been set forth above. Essentially, Katsuma et al. teach a novel transdermal therapeutic preparation, which can efficiently deliver a pharmaceutically active agent into the living body. Katsuma et al. teach that the transdermal preparation is a highly safe and administration-controllable delivery system, in which the transdermal drug absorption-enhancing property of highly safe terpenes is effectively exerted in the delivery system without causing irritation to the skin, even in the presence of ethanol as solvent (page 2, lines 3-5 and 50-58).

Katsuma et al. teach that the transdermal absorption preparation comprises a pharmaceutical active agent for hyperlipedemia use, i.e. pravastatin sodium and the like (page 5: line 26). Katsuma et al. also teach that the transdermal absorption preparation also comprises a monoterpene, or a combination of monoterpene, which acts as a transdermal absorption enhancing agent, wherein the monoterpene can be from essential oils that contain monoterpenes as main components (page 3, lines 9 and 20). Katsuma et al. further teach that suitable monoterpenes can be those having cyclic hydrocarbon structures, i.e. limonene and pinene, or linear monoterpenes having an aldehyde or a hydroxyl group, i.e. citral or citronellol. In addition, cyclic monoterpenes having a hydroxyl group, i.e. menthol and terpineol, are also useful as the transdermal absorption enhancing agent (page 3, lines 9-20 and 36-40, and structures below):



Katsuma et al. also teach that the transdermal absorption preparation is for external purpose (page 5, line 48), in which the external preparation dramatically improves the skin penetration of drugs that are generally considered having relative low skin penetration ability to a great extent (page 21, lines 9-12).

With respect to the recitation of the external preparation of claim 1 is a plaster or a poultice, as claimed in claims 18 and 19, it is noted that the prior art Katsuma et al. do not teach that the transdermal absorption preparation is used in the same manner as claimed in claims 18-19; however, the intended use of the claimed external preparation does not patentably distinguish the composition, per se, since such undisclosed use is inherent in the reference composition. In order to be limiting, the intended use must create a structural difference between the claimed composition and the prior art composition. In the instant case, the intended use does not create a structural difference, thus the intended use is not limiting.

Osborne et al. teach a bio-adhesive formulation, i.e. pharmaceutical gel formulation or dermatological formulation that are capable of delivery drugs of varying solubility

characteristics, wherein the formulations are suitable for applying to a skin surface (Abstract and column 2, lines 20-24; column 12, lines 48-50).

Osborne et al. teach that from a practical point-of-view, increased water content is desirable because when a subject administers a formulation to skin or mucosal surfaces, it is desirable that the formulation is not dehydrating and preferably moisturizing to prevent not only topical reactions to the formulations but also to keep the formulation adhering to the application site. Formulations containing non-aqueous solvents such as ethanol may give rise to this problem because ethanol is a dehydrating agent.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

However, Katsuma et al. and Osborne et al. combined do not teach the instantly claimed additional components, i.e. liquid paraffin, styrene-isoprene-styrene copolymer or salicylic saturated hydrocarbon resin, and those as claimed in claims 21-22, 26-27. The deficiency is cured by Sawayanagi et al. and Hidaka et al. combined.

Sawayanagi et al. teach a plaster preparation, which is suitable for cutaneous application, comprising a water-soluble polymer, i.e. sodium polyacrylate; an absorbefacient for promoting cutaneous absorption, i.e. propylene glycol, 1-menthol; optional additives which include: polyhydric alcohols, i.e. sorbitol; inorganic fillers, i.e. kaolin; surfactants, i.e. polyethylene glycol monolaurate; pH modifiers and the like; hydrophobic polymers, i.e. styrene-isoprene-styrene block copolymer; additional additives, i.e. aliphatic hydrocarbon resins; plasticizer, i.e. liquid paraffin (entire column 2; column 3, lines 1-14).

Hidaka et al. teach a pharmaceutical plaster, which is capable of enhancing the absorption for clinically effective drugs for human skin application, comprising inorganic fine particles, i.e. silicate salts or aluminosilicate compounds; a usual adhesive, i.e. polyisoprene rubber; diffusion auxiliary, i.e. polyethylene glycol, sorbitol, fluid paraffin, water (column 3, lines 45-49; column 4, lines 17-19; column 6, lines 12-14; column 7, lines 15-18; column 14, lines 56-66).

Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)

It would have been obvious to a person of ordinary skilled in the art at the time the invention was made to combine the teaching of Katsuma et al. and Osborne et al. with Sawayanagi et al. and Hidaka et al. to arrive at the instant invention.

One of ordinary skill would have been motivated to incorporate the additional components, i.e. liquid paraffin, styrene-isoprene-styrene copolymer or salicylic saturated hydrocarbon resin, into the external preparation because the prior art, namely Sawayanagi et al. and Hidaka et al., teach that these components are commonly known in the art and are suitable ingredients for use in skin plaster preparation; and thus it would have been obvious for one of ordinary skill to employ. With respect to the amount of each of these additives, it is a routine optimization and would been obvious for one of ordinary skill in the art to try and adjust to the desirable amount.

From the teaching of the references, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed external formulation. Therefore, the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed on 02/23/2009 with respect to claims **1, 4, 7-24** have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are allowed.

Applicants' amendments necessitated the new grounds of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication from the Examiner should direct to Helen Mei-Ping Chui whose telephone number is 571-272-9078. The examiner can normally be

reached on Monday-Thursday (7:30 am – 5:00 pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where the application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either PRIVATE PAIR or PUBLIC PAIR. Status information for unpublished applications is available through PRIVATE PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the PRIVATE PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/H. C./

Examiner, Art Unit 1616

/Mina Haghighatian/

Primary Examiner, Art Unit 1616